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Synthesis of new optically active polycyclic N-heterocycles derived from L-prolinamine[1]

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Abstract

The *N*-Boc-protected (*S*)-prolinamine reacts easily with formaldehyde and diverse α-hydroxyimino ketones to give imidazole *N*-oxides with an enantiomerically pure *N*-protected (pyrrolidin-2-yl)methyl substituent. Subsequent deprotection yields the corresponding NH derivatives. Upon treatment of these products with Ac_2O at room temperature, a cascade of reactions leads to optically active tricycyclic products. In all these processes, the stereogenic centre is preserved. In one case, the bis-heterocyclic imidazole *N*-oxide was transformed to the corresponding optically active imidazole-2-thione via the sulfur-transfer reaction with 2,2,4,4-tetramethylcyclobutane-1,3-dithione.

1. Introduction

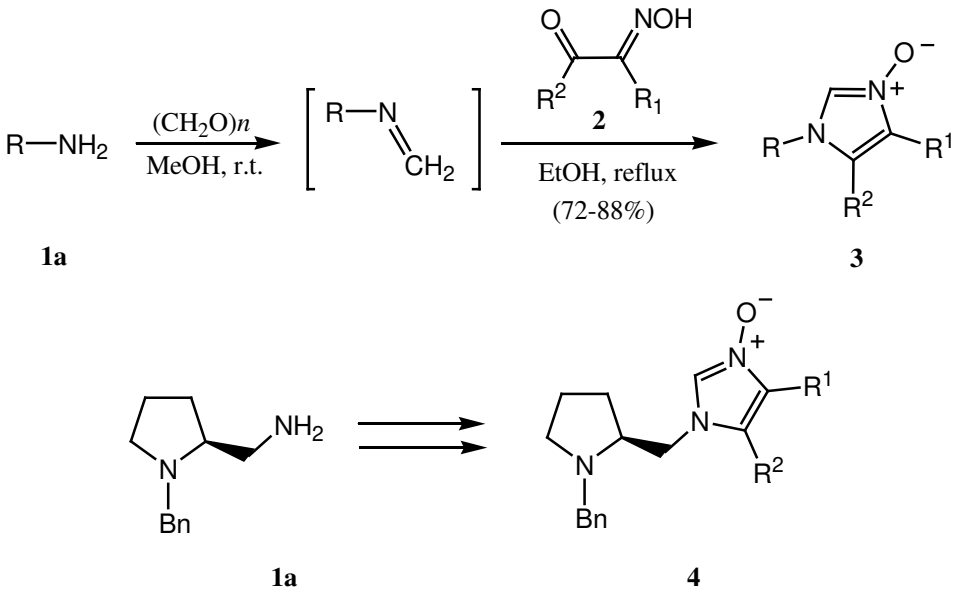
The pyrrolidine system is well known as an important structural unit of organic molecules with biological activity.[2] Moreover, optically active pyrrolidine-containing compounds derived from proline are with fundamental importance for the preparation of most efficient ligands and organocatalysts.[3] However, relatively little is known about the synthesis and applications of enantiomerically pure bis-heterocycles containing the pyrrolidine ring. In a series of recent publications, we reported syntheses of optically active imidazole derivatives, and the method used was based on a cyclization reaction, in which primary aliphatic amines **1** and α-hydroxyimino ketones **2** were the starting materials for the preparation of imidazole *N*-oxides **3**[4] (Scheme 1).

Searching for new primary amines, which can be used in this procedure as a chirality platform, we recently applied *N*-protected 'prolinamine' (2-(aminomethyl)pyrrolidine, **1a**) to prepare a number of bisheterocycles of type **4**, in which an imidazole *N*-oxide function was present.[5] These products can easily be converted into other imidazole derivatives such as imidazole-2-thiones, imidazol-2-ones, or deoxygenated analogs.[4,5] Regarding the efficiency of pyrrolidine-derived organocatalysts, an important feature of the structure is the substitution pattern of the N-atom. For the reactions, which occur via iminium salts, the non-protected N-atom is with vital importance. In the previous paper,[5] we described the synthesis and selected conversions of *N*-benzyl-substituted bis-heterocycles **4**, which subsequently should be

deprotected by treatment either with Raney-Ni or by hydrogenation over Pd/C. In both cases, the reaction results in the deoxygenation of the imidazole oxide. In the hydrogenation experiment, the deoxygenation occurred simultaneously with the debenzylation.[5]

In order to elaborate a protocol for the selective deprotection of imidazole *N*-oxides of type **4**, we report now on the application of *N*-Boc-protected proline amine in the multistep synthesis leading to these compounds.

Scheme 1

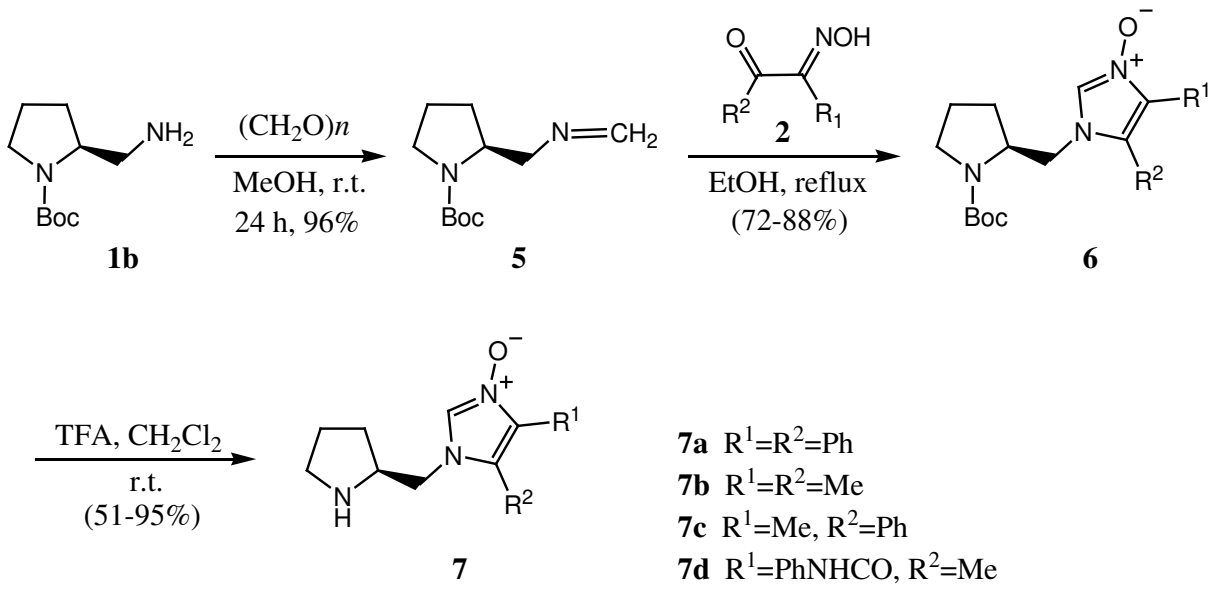


2. Results and discussion

The starting material, *N*-Boc-protected (*S*)-proline amine (**1b**), was obtained from (*S*)-proline via Boc-protection, reduction of the carboxyl group, replacement of the hydroxy by the azido group, and reduction of the latter, based on the recently published procedures.[6] Subsequently, amine **1b** was treated with paraformaldehyde in methanol yielding the corresponding imine **5** [7], which was the starting material for the reaction with α-hydroxyimino ketones **2**, leading to the N-Boc-protected bis-heterocyclic *N*-oxides **6** (Scheme 2). The latter were obtained as crystalline materials, and their structure was confirmed by their spectroscopic data. In all cases, the bridging CH_2 group appeared in the ^1H NMR spectrum as an AB system, and the most

characteristic signal of H-C(2) of the imidazole ring was found downfield-shifted at 7.79-8.08 ppm.

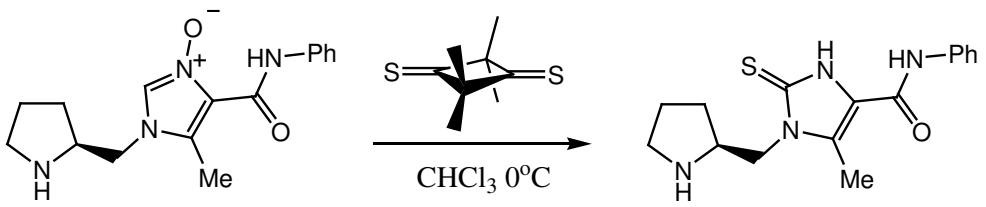
Scheme 2



Characteristically, in the ^{1}H NMR spectra of *N*-oxides **6** in $CDCl_3$ at room temperature, the signal of the Boc group was broadened. However, it appeared as a sharp signal when the spectra were registered in DMSO-d_6 at 80^{o}C.

The deprotection of the pyrrolidine N-atom in compounds **6** was smoothly performed using trifluoroacetic acid (TFA) in CH_2Cl_2 solution at room temperature. In contrast to the attempted debenzylations,[5] in all cases studied the *N*-oxide function in the imidazole ring was preserved and, therefore, the *N*-deprotected bis-heterocycles **7** could be used for further transformations of the imidazole moiety. Thus, treatment of **7d** with 2,2,4,4-tetramethylcyclobutane-1,3-dithione[9] in $CHCl_3$ at 0 ^{o}C led to the imidazole-2-thione derivative **8** (Scheme 3). This so-called sulfur-transfer reaction is well established for 2-unsubsituted imidazole *N*-oxides[4,5] and offers a straight-forward access to biologically active imidazole-2-thione derivatives.[10]

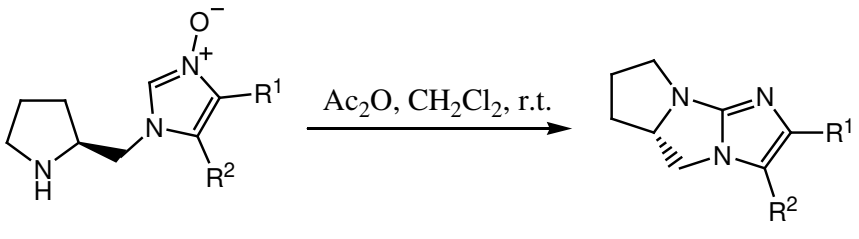
Scheme 3



7d **8**

As reported in a previous publication, treatment of 2-unsubstitued imidazole *N*-oxides with Ac_2O, depending on the reaction conditions, leads to isomeric imidazol-2-ones or their *N*-acetylated derivatives.[11] In a series of experiments, the N-oxides **7** in CH_2Cl_2 were treated with Ac_2O at room temperature, and the products **9**, isolated as viscous oils, did not contain C=O groups (IR). In addition, the ^1H NMR spectra proved the absence of the characteristic signal of the imidazole H-C(2). Furthermore, the comparison of the signal pattern in the aliphatic region displayed by compounds **7** and the new products **9** suggested a substantial change in the structures. The appearance of a signal located at 159.1 ppm in the ^{13}C NMR spectrum of **9a** suggested the presence of a C=N group. Finally, the ESI-MS of **9a** with *m/z* = 302.16494 ($[M+1]^+$) evidenced the molecular mass of $C_{20}H_{19}N_3$, which can be attributed to a product formed from **7a** via formal loss of H_2O. Based on these data, the tricyclic structure **9a** being the product of the heterocyclization of the starting N-oxide, is proposed (Scheme 4). The analogous products **9b**-**9d** were obtained starting with the N-oxides **7b-7d**, respectively.

Scheme 4

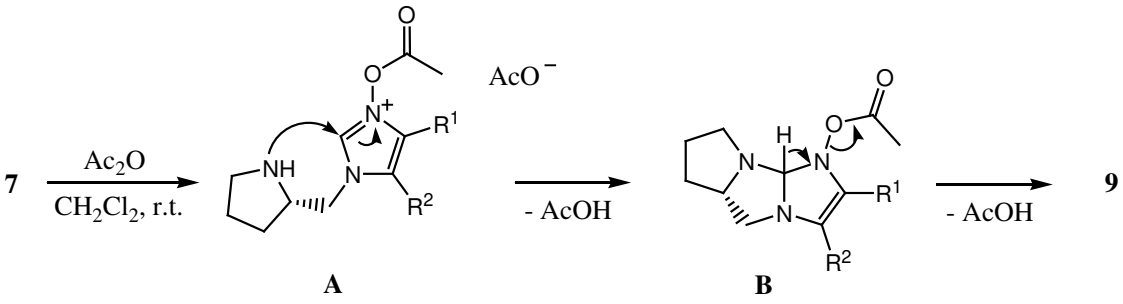


7

9a R^1=R^2=Ph
9b R^1=R^2=Me
9c R^1=Me, R^2=Ph
9d R^1=PhNHCO, R^2=Me

The proposed reaction pathway leading to the unknown tricyclic products **9** is presented in Scheme 5. Apparently, the initial acetylation occurs at the *N*-oxide group, and the intermediate cation **A** undergoes the heterocyclization to give **B**, which rearomatizes via elimination of AcOH. An analogous explanation for the heterocyclization observed in the case of 1-(β-hydroxypropyl)-imidazol-3-oxide upon treatment with Ac_2O was described recently.[12] Another case of the activaction of C(2) in imidazole *N*-oxides towards the nucleophilic addition of water was reported for the reaction with electron-deficient 2,2-bis(trifluoromethyl)ethane-1,1-dicarbonitrile.[13]

Scheme 5



3. Conclusion

The results of this study show that bis-heterocycles containing the non-protected pyrrolidine and imidazole *N*-oxide linked via a methylene group can be prepared from *N*-Boc-protected prolinamine in an enantiopure form. The deprotection of the pyrrolidine ring with TFA occurs without change of the *N*-oxide moiety. Treatment of the *N*-oxide derivatives containing the non-protected pyrrolidine ring with Ac_2O leads to the hitherto unknown tricyclic N-heterocycles identified as 5*H*-pyrro[1,2-*c*]imidazo[1,2-*a*]imidazole derivatives. The obtained enantiomerically pure products are of interest as potential ligands for asymmetric synthesis. Similar byciclic systems derived from proline are reported as prone catalysts for, e.g., desymmetrization of *meso*-1,2-diols.[14]

4. Experimental

4.1. General

Melting points were determined in a capillary using a Melt-Temp. II apparatus (Aldrich) or STUART SMP30 and are uncorrected. The IR Spectra were recorded on a NEXUS FT-IR spectrophotometer in KBr; absorptions in cm^{-1}. The ^{1}H and $^{13}C\{1H\}$ NMR spectra were measured on a Bruker Avance III instrument (600 and 150 MHz, resp.) using solvent signal as reference. Multiplicity of signals in the ^{13}C NMR spectra was established using the HMQC technique. Chemical shifts (δ) are given in ppm and coupling constants J in Hz. Assignments of signals in ^{13}C NMR spectra were made on the basis of HMQC experiments. HR-MS: Bruker maxis spectrometer; ESI-MS: Varian 500 instrument. Optical rotations were determined on a PERKIN-ELMER 241 MC polarimeter for λ = 589 nm.

4.2 General procedure for the synthesis of compounds 6.

To the solution of Boc-prolinamine (200.0 mg, 1.0 mmol) in MeOH (3 mL) paraformaldehyde (30.0 mg, 1.10 mmol) was added at room temperature and the mixture was stirred over night. Then, the solvent was evaporated and the obtained imine was dissolved in EtOH (4 mL). To this solution, an equimolar amount of the corresponding α-hydroxyimino ketone was added and the mixture was heated at reflux for 3 h. Next, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography or by crystallization.

4.2.1. 1-{[(2*S*)-*N*-Boc-pyrrolidin-2-yl]methyl}-4,5-diphenyl-1*H*-imidazole 3-oxide (6a). Yield: 0.348 g (83%). Colorless crystals. Mp. 218–220°C (Et_2O). IR (KBr): ν 3420br, 2974m, 1682s, 1393m, 1363m, 1183m, 1122m, 1090m, 978m, 753m. ^{1}H NMR ($CDCl_3$): δ 8.08 (s, 1H, HC(2)); 7.55–7.51 (m, 2H, HC(arom.)); 7.45–7.41 (m, 3H, HC(arom.)); 4.08–4.72 (m, 1H, HC(2'), 2H, H_2C); 3.36–2.98 (m, 1H, HC(5')); 1.88–1.64 (m, 1H, H_2C(3'), 1H, H_2C(4')); 1.45 (s, 9H, *t*-Bu); 1.43–1.32 (m, 1H, H_2C(3'), 1H, H_2C(4')). ^{13}C NMR ($CDCl_3$): δ 155.0 (C=O); 131.1 (CH(arom.)); 130.6 (C(arom.)); 129.8, (CH(arom.)); 129.7 (C(arom.)); 129.4 (CH(arom.)); 128.3 (C(imid.)); 128.2 (CH(arom.)); 127.7, 127.6, 127.0 (C(arom.)); 126.4 (C(2)); 80.6 (Me_3C); 57.4 (C(2')); 47.6 (CH_2); 47.1 (C(5')); 28.7 (Me_3C); 22.7 (C(3')); 22.7 (C(4')). HR-ESI-MS (MeOH + HCOOH): 420.22828 (calcd 420.22817 for $C_{25}H_{30}N_3O_3$, $[M+1]^+$). $[\alpha]_D^{25}$ = –8 (c 0.625, CH_2Cl_2).

4.2.2. 1-{[(2*S*)-*N*-Boc-pyrrolidin-2-yl]methyl}-4,5-dimethyl-1*H*-imidazole 3-oxide (6b). Yield: 0.259 g (88%). Pale yellow oil (SiO_2, AcOEt/MeOH, 7:3 (+Et_3N)). IR (film): ν 3397–2931br, 1689m, 1456m, 1405m, 1341m, 1170m, 1107m, 976m, 773m. ^{1}H NMR ($CDCl_3$): δ 7.94 (s, 1H, HC(2)); 4.10–3.70 (m, 1H, HC(2'), 2H, H_2C); 3.35–3.08 (m, 2H, H_2C(5')); 2.16 (s, 3H, Me); 2.13 (s, 3H, Me); 1.93–1.61 (m, 2H, H_2C(3'), 2H, H_2C(4')); 1.42 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$): δ 155.0 (C=O); 126.8 (C(imid.)); 125.3 (C(2)); 121.9 (C(imid.)); 80.3 (Me_3C); 57.0 (C(2')); 47.6 (CH_2); 47.1 (C(5')); 28.6 (Me_3C); 27.9 (C(3')); 23.7 (C(4')); 8.9 (Me); 7.4 (Me). HR-ESI-MS (MeOH + NaI): 296.19695 (calcd 296.19687 for $C_{15}H_{26}N_3O_3$, $[M+1]^+$). $[\alpha]_D^{25}$ = –24 (c 0.5, CH_2Cl_2).

4.2.3. 1-{[(2*S*)-*N*-Boc-pyrrolidin-2-yl]methyl}-4-methyl-5-phenyl-1*H*-imidazole 3-oxide (6c). Yield: 0.275 g (77%). Pale yellow oil (SiO_2, AcOEt/MeOH, 1:1 (+Et_3N)). IR (film): ν 3390–2976br, 1683m, 1456m, 1397m, 1366m, 1167m, 1105m, 975m, 766m. ^{1}H NMR ($CDCl_3$): δ 7.91 (s, 1H, HC(2)); 7.53–7.45 (m, 3H, HC(arom.)); 7.32–7.26 (m, 2H, HC(arom.)); 4.10–3.70 (m, 2H, H_2C, 1H, HC(2')); 3.32–2.94 (m, 2H, H_2C(5')); 2.21 (s, 3H, Me); 1.83–1.60 (m, 1H, H_2C(3'), 1H, H_2C(4')); 1.42 (s, 9H, *t*-Bu); 1.37–1.23 (m, 1H, H_2C(3'), 1H, H_2C(4')). ^{13}C NMR ($CDCl_3$): δ 155.0 (C=O); 130.6 (CH(arom.)); 129.6 (C(imid.)); 129.4 (CH(arom.)); 128.3 (C(imid.)); 127.7 (C(arom.)); 127.1 (CH(arom.)); 125.5 (C(2)); 81.2 (Me_3C); 57.3 (C(2')); 47.3 (CH_2); 47.1 (C(5')); 28.6 (3 CH_3); 23.6 (C(3')); 22.6 (C(4')); 7.9 (Me). HR-ESI-MS (MeOH + NaI): 358.21273 (calcd 358.21252 for $C_{20}H_{28}N_3O_3$, $[M+1]^+$). $[\alpha]_D^{25}$ = +99 (c 0.25, CH_2Cl_2).

4.2.4. *N*-Phenyl-1-{[(2*S*)-*N*-Boc-pyrrolidin-2-yl]methyl}-5-methyl-1*H*-imidazole-4-carboxamide 3-oxide (6d). Yield: 0.288 g (72%). Colorless crystals. Mp. 208–210°C (Et_2O). IR (KBr): ν 3439br, 2983m, 1698m, 1598m, 1390m, 1311m, 1167m, 1122m, 759m. ^{1}H NMR ($CDCl_3$): δ 12.91 (s, 1H, NH); 7.79 (s, 1H, HC(2)); 7.72–7.68 (m, 2H, HC(arom.)); 7.35–7.30 (m, 2H, HC(arom.)); 7.12–7.07 (1H, HC(arom.)); 4.17–3.98 (m, 1H, HC(2'), 2H, H_2C); 3.42–3.23 (m, 2H, H_2C(5')); 2.70 (s, 3H, Me); 2.06–1.96 (m, 1H, H_2C(3')); 1.89–1.80 (m, 1H, H_2C(4')); 1.77–1.71 (m, 1H, H_2C(3')); 1.68–1.59 (m, 1H, H_2C(4')); 1.47 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$): δ

157.6 (C=O); 155.3 (C=O); 138.1 (C(arom.)); 131.9 (C(imid.)); 128.9 (2 CH(arom.)); 125.3 (C(2)); 124.0 (CH(arom.)); 122.1 (C(imid.)); 120.6 (2 CH(arom.)); 81.0 (Me_3C); 57.0 (C(2')); 47.5 (CH_2); 47.2 (C(5')); 28.6 (Me_3C); 28.6 (C(3')); 28.5 (C(4')); 10.2 (Me). HR-ESI-MS (MeOH + HCOOH): 401.21853 (calcd 401.21833 for $C_{21}H_{29}N_4O_4$, $[M+1]^+$). $[\alpha]_D^{25}$ = –12 (c 0.55, CH_2Cl_2).

4.3. General procedure for the synthesis of compounds 7.

To the solution of the corresponding imidazole *N*-oxide **6** (1 mmol) in CH_2Cl_2 (5 mL) trifluoroacetic acid (13 mL) in CH_2Cl_2 (13 mL) was added. After all of **6** was consumed (monitored by TLC) the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (4 mL). Then, $NaHCO_3$ was added and the mixture was magnetically stirred for 3 h. Next, the solid was filtered and the filtrate was concentrated by evaporation in a rotary evaporator. The crude product **7** was purified by column chromatography.

4.3.1. {[(2*S*)-Pyrrolidin-2-yl]methyl}-4,5-diphenyl-1*H*-imidazole 3-oxide (7a). Yield: 0.220 g (69%). Pale yellow oil (SiO_2, AcOEt/MeOH, 1:1 (+Et_3N)). IR (film): ν 3432br, 2979w, 2780m, 2471m, 1675s, 1447m, 1430m, 1205m, 1173w, 1130m, 833m, 798m, 762m, 721m, 704m. ^{1}H NMR ($CDCl_3$): δ 9.24 (s, 1H, HC(2)); 7.50–7.41 (m, 5H, HC(arom.)); 7.37–7.33 (m, 2H, HC(arom.)); 7.31–7.25 (m, 3H, HC(arom.)); 4.58 (dd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 10.2, 1H, H_2C–N); 4.15 (dd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 3.0, 1H, H_2C–N); 3.74–3.66 (m, 1H, HC(2')); 3.11–3.03 (m, 1H, H_2C(5')); 2.98–2.91 (m, 1H, H_2C(5')); 1.95–1.73 (m, 1H, H_2C(3'), 2H H_2C(4')); 1.64–1.55 (m, 1H, H_2C(3')). ^{13}C NMR ($CDCl_3$): δ 131.2, 130.7, 130.4, 130.3, 129.6, 129.1, 129.0, 128.4, 128.0, 126.3, 125.8 (2 C(arom.), 6 CH(arom.), 2 C(imid.), C(2)); 59.3 (C(2')); 47.2 (CH_2); 45.1 (C(5')); 28.4 (C(3')); 23.3 (C(4')). HR-ESI-MS (MeOH + NaI): 320.17559 (calcd 320.17574 for $C_{20}H_{22}N_3O$, $[M+1]^+$). $[\alpha]_D^{25}$ = +81 (c 0.5, CH_2Cl_2).

4.3.2. {[(2*S*)-Pyrrolidin-2-yl]methyl}-4,5-dimethyl-1*H*-imidazole 3-oxide (7b). Yield: 0.185 g (95%). Pale yellow oil (SiO_2, AcOEt/MeOH, 1:1 (+Et_3N)). IR (film): ν 3304br, 2960m, 1688m, 1629m, 1448m, 1382m, 1200m, 1147m, 927m, 731m. ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H, HC(2)); 3.78 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 4.8, 1H,

H_2C–N); 3.72 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 8.4, 1H, H_2C–N); 3.39–3.33 (m, 1H, HC(2')); 2.94–2.86 (m, 2H, H_2C(5')); 2.09 (s, 3H, Me); 2.07 (s, 3H, Me); 1.91–1.84 (m, 1H, H_2C(3')); 1.81–1.73 (m, 1H, H_2C(4')); 1.72–1.64 (m, 1H, H_2C(4')); 1.41–1.33 (m, 1H, H_2C(3')). ^{13}C NMR ($CDCl_3$): δ 126.0 (C(2)); 125.1 (C(imid.)); 121.1 (C(imid.)); 58.0 (C(2')); 50.1 (CH_2); 46.2 (C(5')); 29.0 (C(3')); 25.1 (C(4')); 8.8 (Me); 7.2 (Me). HR-ESI-MS (MeOH + NaI): 196.14431 (calcd 196.14444 for $C_{10}H_{18}N_3O$, $[M+1]^+$). $[\alpha]_D^{25}$ = +53 (c 0.25, CH_2Cl_2).

4.3.3. {[(2*S*)-Pyrrolidin-2-yl]methyl}-4-methyl-5-phenyl-1*H*-imidazole 3-oxide (7c). Yield: 0.164 g (64%). Pale yellow oil (SiO_2, AcOEt/MeOH, 1:1 (+Et_3N)). IR (film): ν 3435br, 3057w, 2776w, 2505w, 1683s, 1446m, 1428m, 1267m, 1201m, 1135m, 1014w, 835m, 798m, 721m, 703m. ^{1}H NMR ($CDCl_3$): δ 9.23 (s, 1H, HC(2)); 7.57–7.53 (m, 3H, HC(arom.)); 7.41–7.37 (m, 2H, HC(arom.)); 4.72 (dd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 10.2, 1H, H_2C–N); 4.30 (dd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 3.0, 1H, H_2C–N); 3.60–3.53 (m, 1H, HC(2')); 3.56–3.40 (m, 1H, H_2C(5')); 3.28–3.21 (m, 1H, H_2C(5')); 2.18 (s, 3H, Me)); 2.12–2.03 (m, 1H, H_2C(3')); 1.97–1.83 (m, 2H, H_2C(4')); 1.72–1.64 (m, 1H, H_2C(3')). ^{13}C NMR ($CDCl_3$): δ 130.9 (CH(arom.)); 130.7 (CH(arom.)); 130.0 (C(arom.)); 129.9 (CH(arom.)); 128.6 (C(imid.)); 127.6 (C(2)); 125.4 (C(imid.)); 59.6 (C(2')); 47.1 (CH_2); 45.2 (C(5')); 28.0 (C(3')); 23.2 (C(4')); 7.4 (Me). HR-ESI-MS (MeOH + HCOOH): 258.16039 (calcd 258.16009 for $C_{15}H_{20}N_3O$, $[M+1]^+$). $[\alpha]_D^{25}$ = +58 (c 0.25, CH_2Cl_2).

4.3.4. *N*-Phenyl-{[(2*S*)-pyrrolidin-2-yl]methyl}-5-methyl-1*H*-imidazole-4-carboxamide 3-oxide (7d). Yield: 0.153 g (51%). Pale yellow oil (SiO_2, AcOEt/MeOH, 1:1 (+Et_3N)). IR (film): ν 3423br, 3140w, 2952m, 2872m, 1659s, 1617m, 1596m, 1563m, 1449m, 1417m, 1309s, 1277s, 1132m, 1105m, 908m, 763s, 695m, 624m. ^{1}H NMR ($CDCl_3$): δ 12.98 (s, 1H, HN); 8.05 (s, 1H, HC(2)); 7.73–7.68 (m, 2H, HC(arom.)); 7.35–7.30 (m, 2H, HC(arom.)); 7.12–7.07 (m, 1H, HC(arom.)); 3.88 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 4.2, 1H, H_2C–N); 3.39 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 8.4, 1H, H_2C–N); 3.47–3.40 (m, 1H, HC(2')); 3.00–2.95 (m, 1H, H_2C(5')); 2.92–2.87 (m, 1H, H_2C(5')); 2.68 (s, 3H, Me); 2.00–1.93 (m, 1H, H_2C(3')); 1.85–1.78 (m, 1H, H_2C(4')); 1.77–1.69 (m, 1H, H_2C(4')); 1.43–1.36 (m, 1H, H_2C(3')). ^{13}C NMR ($CDCl_3$): δ 157.8 (C=O); 138.2, 131.2 (2 C(arom.)); 128.9 (CH(arom.)); 125.8 (C(2)); 124.0

(CH(arom.)); 121.7 (C(arom.)); 120.6 (CH(arom.)); 57.5 (C(2')); 50.6 (CH_2); 46.6 (C(5')); 29.2 (C(3')); 25.8 (C(4')); 9.9 (Me). HR-ESI-MS (MeOH + NaI): 301.16578 (calcd 301.16590 for $C_{16}H_{21}N_4O_2$, $[M+1]^+$). $[\alpha]_D^{25}$ = +28 (c 1.0, CH_2Cl_2).

4.4. *N*-Phenyl-{[(2*S*)-pyrrolidin-2-yl]methyl}-5-methyl-2-thioxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (8). To the solution of imidazole *N*-oxide **7d** (1 mmol) in $CHCl_3$ (4 mL) 2,2,4,4-tetramethylcyclobutanone-1,3-dithione (2 mmol) in $CHCl_3$ (2 mL) was added at 0ºC and the mixture was stirred over night. Then, the solvent was removed and the residue was washed with hexane. Yield of **8**: 0.193 g (61%). Colorless crystals. Mp. 234°C (decomp., hexane). IR (KBr): ν 3432br, 3325m, 2920m, 1683m, 1659m, 1592m, 1513m, 1432m, 1205m, 1185m, 1136m, 1066m, 804m, 725m. ^{1}H NMR (DMSO-d_6): δ 9.55 (s, 1H, HN); 7.69–7.65 (m, 2H, HC(arom.)); 7.36–7.32 (m, 2H, HC(arom.)); 7.11–7.06 (m, 1H, HC(arom.)); 4.06 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 4.4, 1H, H_2C–N); 3.90 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 8.8, 1H, H_2C–N); 3.69–3.64 (m, 1H, HC(2')); 2.92–2.85 (m, 2H, H_2C(5')); 2.53 (s, 3H, Me); 1.89–1.76 (m, 1H, H_2C(4'), 1H, H_2C(3')); 1.69–1.61 (m, 1H, H_2C(4')); 1.55–1.48 (m, 1H, H_2C(3')). ^{13}C NMR (DMSO-d_6): δ 160.6 (C=S); 158.5 (C=O); 139.2 (C(arom.)); 134.1 (C(imid.)); 129.2 (2 CH(arom.)); 129.0 (C(imid.)); 123.9 (CH(arom.)); 120.0 (2 CH(arom.)); 58.3 (C(2')); 47.6 (CH_2); 45.9 (C(5')); 29.1 (C(3')); 25.6 (C(4')); 10.8 (Me). HR-ESI-MS (MeOH + NaI): 317.14331 (calcd 317.14306 for $C_{16}H_{21}N_4OS$, $[M+1]^+$). $[\alpha]_D^{25}$ = +16 (c 1.0, DMSO).

4.5. General procedure for the synthesis of compounds 9.

To a solution of the corresponding imidazole *N*-oxide **7** (1 mmol) in CH_2Cl_2 (5 mL), freshly distilled acetic anhydride (10 mL) was added at room temperature. After all of **7** was consumed (monitored by TLC), MeOH (5 mL) was added to the solution and stirring was continued for 10 min. Next, the solvent was evaporated and the crude product was purified by column chromatography (AcOEt/hexane 3:7).

4.5.1. (5a*S*)-2,3-Diphenyl-5a,6,7,8-tetrahydro-5*H*-pyrrolo[1,2-*c*]imidazo[1,2-*a*]imidazole (9a). Yield: 0.216 g (72%). Colorless oil (SiO_2, AcOEt/MeOH, 7:3). IR (film): *ν* 3412br, 2927m, 1671m, 1602m, 1447m, 1335m, 1212m, 1071m, 771m, 699m. ^{1}H NMR ($CDCl_3$): δ 7.54–7.51 (m, 2H, HC(arom.));

7.34–7.31 (m, 2H, HC(arom.)); 7.28–7.15 (m, 4H, HC(arom.)); 7.17–7.11 (m, 2H, HC(arom.)); 4.42–4.36 (m, 1H, HC(2')); 4.17–4.11 (m, 1H, H_2C); 3.88–3.83 (m, 1H, H_2C); 3.65–3.59 (m, 1H, $H_2C(5')$); 3.42–3.37 (m, 1H, $H_2C(5')$); 2.16–2.10 (m, 1H, $H_2C(3')$); 2.03–1.90 (m, 2H, $H_2C(4')$); 1.69–1.61 (m, 1H, $H_2C(3')$). ^{13}C NMR ($CDCl_3$): δ 159.1 (C=N); 139.1 (1 C(arom.)); 135.2, 131.1 (2 C(imid.)); 128.8, 128.2, 128.1, 127.2, 126.4 (10 CH(arom.)); 121.8 (1 C(arom.)); 67.7 (C(2')); 50.8 (C(5')); 48.3 (CH_2); 31.8 (C(3')); 26.1 (C(4')). HR-ESI-MS (MeOH + HCOOH): 302.16494 (calcd 302.16517 for $C_{20}H_{20}N_3$, $[M+1]^+$). $[\alpha]_D^{25}$ = –35 (c 0.25, CH_2Cl_2).

4.5.2. (5a*S*)-2,3-Dimethyl-5a,6,7,8-tetrahydro-5*H*-pyrrolo[1,2-*a*]imidazo[1,2-*a*]imidazole (9b). Yield: 0.120 g (68%). Colorless oil (SiO_2, AcOEt/hexane, 3:7). IR (film): ν 3403br, 2969m, 1686m, 1423m, 1320m, 1142m, 1011m, 806m, 731m, 650m. ^1H NMR ($CDCl_3$): δ 4.33–4.28 (m, 1H, HC(2')); 3.98–3.94 (m, 1H, H_2C); 3.68–3.65 (m, 1H, H_2C); 3.46–3.41 (m, 1H, $H_2C(5')$); 3.29–3.24 (m, 1H, $H_2C(5')$); 2.10–2.04 (m, 1H, $H_2C(3')$); 2.06 (s, 3H, Me); 2.03 (s, 3H, Me); 1.92–1.84 (m, 2H, $H_2C(4')$); 1.61–1.54 (m, 1H, $H_2C(3')$). ^{13}C NMR ($CDCl_3$): δ 137.2 (C=N); 131.0 (C(imid.)); 115.3 (C(imid.)); 68.1 (C(2')); 50.6 (C(5')); 47.3 (CH_2); 31.7 (C(3')); 26.0 (C(4')); 11.6 (Me); 8.3 (Me). HR-ESI-MS (MeOH + HCOOH): 178.13416 (calcd 178.13387 for $C_{10}H_{16}N_3$, $[M+1]^+$). $[\alpha]_D^{25}$ = –31 (c 0.4, CH_2Cl_2).

4.5.3. (5a*S*)-2-Methyl-3-phenyl-5a,6,7,8-tetrahydro-5*H*-pyrrolo[1,2-*c*]imidazo[1,2-*a*]imidazole (9c). Yield: 0.188 g (79%). Colorless oil (SiO_2, AcOEt/MeOH, 7:3). IR (film): ν 3420br, 2929m, 1683s, 1447m, 1390m, 1201m, 1130m, 765m, 704m. ^1H NMR ($CDCl_3$): δ 7.42–7.38 (m, 2H, HC(arom.)); 7.34–7.31 (m, 2H, HC(arom.)); 7.27–7.23 (m, 1H, HC(arom.)); 4.42–4.36 (m, 1H, HC(2')); 4.25–4.20 (m, 1H, H_2C); 3.90–3.86 (m, 1H, H_2C); 3.59–3.53 (m, 1H, $H_2C(5')$); 3.38–3.33 (m, 1H, $H_2C(5')$); 2.32 (s, 3H, Me); 2.16–2.08 (m, 1H, $H_2C(3')$); 2.00–1.90 (m, 2H, $H_2C(4')$); 1.66–1.58 (m, 1H, $H_2C(3')$). ^{13}C NMR ($CDCl_3$): δ 158.7 (C=N); 136.2 (1 C(arom.)); 131.1 (C(imid.)); 128.7 (2 CH(arom.)); 126.6 (2 CH(arom.)); 126.1 (1 CH(arom.); 121.3 (C(imid.)); 67.7 (C(2')); 50.6 (C(5')); 49.0 (CH_2); 31.8 (C(3')); 26.0 (C(4')); 14.3 (Me). HR-ESI-MS: 239.14214 (calcd 239.14224 for $C_{15}H_{17}N_3$, $[M]^+$). $[\alpha]_D^{25}$ = –229 (c 0.25, CH_2Cl_2).

4.5.4. *N*-Phenyl-*[*(5a*S*)-3-methyl-5a,6,7,8-tetrahydro-5*H*-pyrrolo[1,2-*c*]imidazo[1,2-*a*]imidazole]-2-carboxamide (9d). Yield: 0.194 g (69%). Colorless oil (SiO_2, AcOEt/MeOH, 7:3). IR (film): ν 3382br, 2973m, 1663m, 1582m, 1570m, 1439m, 1417m, 1338m, 1304m, 1205m, 1056m, 1024m, 756m, 660m. ^{1}H NMR ($CDCl_3$): δ 8.86 (s, 1H, HN); 7.69–7.65 (m, 2H, HC(arom.)); 7.33–7.28 (m, 2H, HC(arom.)); 7.07–7.02 (m, 1H, HC(arom.)); 4.41–4.34 (m, 1H, HC(2')); 4.09–4.04 (m, 1H, H_2C); 3.81–3.76 (m, 1H, H_2C); 3.50–3.44 (m, 1H, $H_2C(5')$); 3.37–3.32 (m, 1H, $H_2C(5')$); 2.50 (s, 3H, Me); 2.17–2.11 (m, 1H, $H_2C(3')$); 2.00–1.90 (m, 2H, $H_2C(4')$); 1.63–1.55 (m, 1H, $H_2C(3')$). ^{13}C NMR ($CDCl_3$): δ 162.2 (C=O); 156.4 (C=N); 138.7 (C(arom.)); 131.8 (C(imid.)); 128.8 (2 CH(arom.)); 127.7 (C(imid.); 123.2 (1 CH(arom.); 119.5 (2 CH(arom.)); 67.7 (C(2')); 50.7 (C(5')); 46.4 (CH_2); 31.7 (C(3')); 26.0 (C(4')); 10.1 (Me). HR-ESI-MS (MeOH + HCOOH): 283.15528 (calcd 283.15534 for $C_{16}H_{19}N_4O$, $[M+1]^+$). $[\alpha]_D^{25} = -86$ (c 0.375, CH_2Cl_2).

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